



NOTES PHAGOCYTE DEFICIENCIES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- *Inherited immunodeficiency disorders*: mutations in genes that code immune-cell functioning
- *Impaired immune function*: recurrent, often severe, life-threatening infections

SIGNS & SYMPTOMS

- Recurrent infection history

DIAGNOSIS

- Characteristic findings upon physical examination

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Genetic testing

TREATMENT

MEDICATIONS

- Infection prophylaxis/treatment

OTHER INTERVENTIONS

- Hematopoietic cell transplantation

CHEDIAK–HIGASHI SYNDROME

osms.it/chediak-higashi_syndrome

PATHOLOGY & CAUSES

- Rare, inherited immunodeficiency disorder; impaired leukocyte lysosomal granules function in phagocytes, NK cells → recurrent pyogenic infections
- **Autosomal recessive**; lysosomal trafficking regulator gene *CHS1/LYST* defect
 - **Trafficking**: protein movement within cell
- Genetic mutation → impaired trafficking → absent/partially functioning *CHS1/LYST* protein → large, abnormal intracellular granules → decreased phagocytosis → infections primarily affect skin, mucous

membranes, respiratory tract

- **Accelerated disease phase**: profound lymphohistiocytic organ infiltration, worsening immunodeficiency

RISK FACTORS

- Parental consanguinity

COMPLICATIONS

- Related to impaired intracellular trafficking
 - Oculocutaneous **albinism** (reduced skin, eye pigment)
 - Neurologic abnormalities
 - **Coagulation defects**

VISIT...

LANZAROTE
Caliente.COM

- Hemophagocytic **lymphohistiocytosis** (disorder resembles lymphoma)
- If bone marrow transplant unsuccessful → childhood death from infection usually occurs

SIGNS & SYMPTOMS

- **Presents in infancy:** frequent/severe bacterial, viral, fungal infections
- **Neurological:** nystagmus, ataxia, **peripheral neuropathy**, seizures, Parkinsonian-like features may develop
- Coagulation defect presents as easy bruising
- Photosensitivity
- Hair has silvery tint

DIAGNOSIS

LAB RESULTS

- **Microscopic hair examination:** pigmentation clumping
- CBC: neutropenia
- **Peripheral blood smear analysis:** **giant** intracellular **granules**
- **Bone marrow aspiration:** large inclusion bodies in precursor cells
- Genetic testing

TREATMENT

MEDICATIONS

- Prophylactic antibiotics
- Prompt, aggressive infection treatment

OTHER INTERVENTIONS

- Hematopoietic cell transplant; cord blood transplant
 - Does not address debilitating neurological manifestations/albinism

CHRONIC GRANULOMATOUS DISEASE (CGD)

osms.it/chronic-granulomatous-disease

PATHOLOGY & CAUSES

- Rare immune-system disorder; affects neutrophils, monocytes, macrophages → serious, life-threatening infections (bacterial/fungal), granuloma formation
 - **X-linked:** CYBB encoded
 - Autosomal recessive form common with consanguinity—CYBA encoded
 - De novo mutations also occur
- **Mutations:** genes encoding for phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which catalyzes lysosomal reactive oxygen species
- Impaired NADPH → phagocytes unable to effectively phagocytize, destroy certain microbes → ↑ infection susceptibility; especially catalase-positive bacteria/fungi

Host immune system response

- Recruiting additional phagocytes, activating T cells
- Immune cells collect around microbe → granulomas form
- Childhood/adulthood diagnosis (underlying mutation-dependent)

Frequent infection sites

- Lung, skin, lymph nodes, liver

Common infections

- Pneumonia, bacteremia, fungemia, impetigo, cellulitis, granulomatous lesions (skin, organs), gingivitis, gastroenteritis, otitis

Inflammation manifestations

- Esophageal/urethral strictures, colitis, cystitis, interstitial pneumonitis, dermatosis

SIGNS & SYMPTOMS

- History of disorder-characteristic recurrent infections, granulomatous lesions
- Fever, leukocytosis, lymphadenopathy, abnormal wound healing, diarrhea, chronic disease anemia, growth failure (children)

DIAGNOSIS

LAB TESTS

- ↑ **inflammation markers:** erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Immune stimulation → hypergammaglobulinemia
- **Neutrophil function tests:** e.g. dihydrorhodamine (DHR) 123 test measure neutrophils ability to produce oxidative burst
- Genetic testing

TREATMENT

MEDICATIONS

- Antimicrobial prophylaxis using combination of therapies
 - **Antibacterial:** TMP/SMX
 - **Antifungal:** itraconazole
 - **Immunomodulatory:** interferon-gamma
- Aggressive acute infection treatment
- **Inflammatory manifestations:** oral glucocorticoids
- Avoid live bacterial vaccines

OTHER INTERVENTIONS

- Hematopoietic cell transplantation: curative if successful

LEUKOCYTE ADHESION DEFICIENCY (LAD)

osms.it/leukocyte-adhesion-deficiency

PATHOLOGY & CAUSES

- Rare, inherited immunodeficiency disorders; mutations in genes encoding leukocyte adhesion molecules → impaired leukocyte function, deficient immunological response (foreign antigens), ↓ inflammatory response to injury
 - **Autosomal recessive** inheritance
- Leukocyte adhesion cascade initiated in response to infection/injury
 - Involves adhesion molecule-activation on vascular endothelial cells which bind to glycoproteins on leukocyte surface
- Stepwise adhesion, activation process
 - **Capture**: temporary leukocyte to endothelial cell tethering
 - **Rolling**: leukocyte rolls along endothelial cells (weak, reversible initial adherence)
 - **Slow rolling**: endothelial cell ligands interact with leukocyte selectins → slow movement along vessel wall
 - **Firm adhesion**: leukocyte integrins bind to endothelial intercellular adhesion molecules (ICAMs) → leukocyte stops (arrest) on endothelial surface
 - **Transmigration**: leukocyte movement between endothelial cells, into interstitium/infected tissue
- **LAD II**: guanosine diphosphate (GDP)-fucose transporter gene (SLC35C1) mutation → absent ligands for selectins
 - **Selectins**: endothelial, leukocyte adhesion glycoproteins that mediate margination, leukocyte rolling (slows velocity → allows endothelial ligand adhesion)
 - Fucose (monosaccharide; cellular glycans, glycolipids component) metabolism defect → absent fucosylated endothelial ligands for selectins
- **LAD III**: mutations in CalDAG-GEF1, kindlin-3; FERMT3 genes → defects all beta integrins (e.g. 1, 2, 3) activation
 - Integrin glycoproteins remain inactivated, unable to adhere to endothelial ligands
 - Beta-3 defect impairs platelet aggregation → severe bleeding tendency
 - Also involves natural killer (NK) cell activity impairment

COMPLICATIONS

- Specific mutation dependent
 - **Poor wound healing**
 - Bleeding tendencies (may involve neonatal cerebral hemorrhage, gastrointestinal tract bleeding)
 - Developmental delay
 - Decreased lifespan (e.g. infection)

TYPES

- **Categorization**: specific genetic defects
- **LAD I**: integrin beta-2 **gene mutation** (ITGB2) **encoding CD18** subunit → CD18 requires activation before endothelial ligand adhesion can occur
 - **Integrins**: glycoproteins that mediate firm adhesion, transmigration along endothelium (via endothelial cell counter-receptors)
 - LAD I defect prevents leukocyte bloodstream → interstitium migration

SIGNS & SYMPTOMS

CLINICAL MANIFESTATIONS OF LAD SYNDROMES

	LAD I	LAD II	LAD III
RECURRENT INFECTIONS	+++	++	+++
GINGIVITIS, PERITONITIS	++	++	-
SKIN INFECTIONS	++	+	++
DELAYED UMBILICAL CORD SEPARATION; OMPHALITIS	+++	+++	+++
INABILITY TO FORM PUS AT INJURY/INFECTION SITE	+++	++	++
IMPAIRED WOUND HEALING	++	++	++
BLEEDING TENDENCIES; PETECHIAE, INTERNAL BLEEDS	-	-	+++
DEVELOPMENTAL MOTOR, INTELLECTUAL DELAY	-	+++	-
OSTEOPOROSIS-LIKE CHARACTERISTICS	-	-	+

DIAGNOSIS

- High index of suspicion at birth with **delayed umbilical cord separation**, leukocytosis, along with additional findings
 - LAD I: **recurrent soft tissue infections**
 - LAD II: psychomotor impairment, Bombay blood group presence
 - LAD III: bleeding complications from birth

LAB RESULTS

- White blood cell count with differential: elevated leukocyte count
 - Leukocytes unable to leave bloodstream → persistent leukophilia (basal) + ↑↑ during infection (especially **neutrophils**)
- Flow cytometry
 - LAD I: CD18, alpha subunit molecules (CD11a, CD11b, CD11c) absence

- LAD-II: SLeX expression (CD15a) absence

- LAD-II: genetic testing confirms defect of gene that encodes for guanosine diphosphate (GDP)-fucose transporter
- LAD III: impaired integrin activation

TREATMENT

MEDICATIONS

- Antibiotics: mild-moderate infections

OTHER INTERVENTIONS

- Control periodontitis: scrupulous oral hygiene, dental care
- Bacterial infection treatment: mitigate severity
- Fucose supplementation (LAD II)
- Hematopoietic cell transplantation